26. (New) The method of Claim 3 wherein the RPE cells and the co-administered cells are attached to a matrix prior to administration.

27. (New) The method of Claim 7 wherein said transplantation of said cells that supply a therapeutic protein or other biologically active molecule is by xenograft.

28. (New) The method of Claim 7 wherein said transplantation of said cells that supply a therapeutic protein or other biologically active molecule is by allograft.

29. (New) The composition of Claim 19 wherein said therapeutic protein, or other biologically active molecule consists of an interleukin, chemokine, interferon, colony stimulating factor or angiogenic factor.

II. REMARKS

Claims 1-24 were pending in this application; claim 24 has been withdrawn from examination as a result of a requirement for restriction under 35 U.S.C. §121. Claims 1-23 have been examined. Claims 1-23 were rejected under 35 U.S.C. §112, first paragraph. Claims 2-7, 9-16 and 19 were rejected under 35 U.S.C. §112, second paragraph. Claims 1-2, 4, 7, 9, 12, 13, 16, 19 and 20 were rejected under 35 U.S.C. §102(b). Claims 1, 2-4, 6, 7, 9, 10, 12, 13, 16-21 and 23 were rejected under 35 U.S.C. §102(e). Claims 1-3, 5, 7, 8, 11, 14, 15 and 22 were variously rejected under 35 U.S.C. §103.

Support for the amendments to the claims and for the new claims is found throughout the specification. Support for the amendments to claims 3, 16, 18 and 23 and for new claims 27 and 28 is found, *inter alia*, on page 7, lines 26 to 28 and page 8, lines 3 to 6. Support for the amendment to claim 19 and for new claims 25 and 29 is found, *inter alia*, in claim 4 as originally filed. Support for new claim 26 is found, *inter alia*, on page on 5, lines 12 to 14.

Thus, the amendments to the claims and the new claims do not constitute new matter. Also, these additions to the claims are to clarify the nature of the invention claimed, and do not constitute and admission that the claims as filed were obvious under 35 U.S.C. §103 in view of cited publications.

Applicants have carefully considered the points raised in the Office Action and believe the Examiner's concerns can be addressed as described herein, thereby placing this case into condition for allowance.

Requirement for Restriction under 35 U.S.C. §121

The Office has required restriction to one of the following groups of claims under 35 U.S.C. § 121:

Group I: Claims 1-23, drawn to a method of administering cells to create an immunologically privileged site; and

Group II: Claim 24, drawn to methods of producing Fas L

In affirmation of the provisional election made on April 1, 1999, Applicants elect with traverse to prosecute the invention of Group I, claims 1-23. Applicants expressly reserve the right under 35 U.S.C. §121 to file a divisional application directed to the nonelected subject matter during the pendency of this application, or an application claiming priority from this application.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-23 were rejected under 35 U.S.C. §112, first paragraph for allegedly not being enabled for the invention as claimed. Applicants respectfully traverse this rejection.

The Examiner's concerns essentially related to the effective "scope" of the enablement, and whether exemplary embodiments adequately supported the invention as claimed. Although the Examiner admits that the specification is enabled "for allogeneic transplantation for at least 8 months," he finds that the specification "does not reasonably provide enablement for any

transplantation in any animal of any sustained period of time" (Office Action, page 4). In particular, it was questioned "whether xenogeneic transplantation using RPE cells could be obtained" (Office Action, page 4).

Applicants believe that the question regarding the use of RPE cells for xenogeneic transplantation does not undermine enablement of the claimed invention when considered in view of the particular factual context of this case, as discussed below.

The invention is based on the discovery that RPE cells secrete FasL. As demonstrated in the specification, RPE cell conditioned media contains FasL and induces apoptosis in activated thymocytes (see sections 6.2.1 and 6.2.2). FasL induces apoptosis in Fas+, antigen-activated T cells to achieve a localized immune suppressive effect.

Expression of FasL appears to be crucial for the maintenance of immune privileged sites and tissues (see, for example, pages 2-3 of the specification; Griffith et al. (1995) *Science* 270:1189-1192 and Streilein (1995) *Science* 270:1158-1159). For example, Streilein reported that FasL positive cells survived indefinitely after an allogeneic transplant whereas FasL negative cells under the same transplant conditions were rejected (p. 1158, second column). The immune suppressive activity associated with FasL is dependent on the presence of Fas on antigen-activated T cells, not on the particular antigen(s) involved in the T cell activation. Thus, the generation of an immune privileged site by RPE cell expression of FasL would be effective for a xenogeneic as well as an allogeneic transplant.

In sum, Applicants' specification provides a presumptively sufficient disclosure. It teaches each and every element of the claimed invention, namely methods to treat a disease in a mammal wherein RPE cells are co-administered with cells that supply a therapeutic or other biologically active molecule. The specification also teaches that the RPE cells are administered in an amount effective to create an immune privileged site and thus allow for the co-administered cells to be allogeneic or xenogeneic to the mammal.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 2-7, 9-16 and 19 were rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Reasons for the rejection of claims 2 and 16 were not stated and therefor, the rejections could not be addressed.

Although Applicants believe that the claims were sufficiently definite in view of the understanding of those of skill in the art, Applicants have attempted to respond to the suggestions of the Examiner in order to enhance clarity and to facilitate disposition of the present case. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

Claims 1-2, 4, 7, 9, 12, 13, 16, 19 and 20 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Ye (1993, *Current Eye Research*, 12:629-639). Applicants respectfully traverse this rejection.

Pending claims of the present invention are directed to methods for treating a disease in a subject by co-administering RPE cells, in an amount effective to create an immunologically privileged site, with cells that supply a therapeutic protein, or other biologically active molecule, in an amount effective to sustain a therapeutic effect. The cells co-administered with the RPE cells that supply the therapeutic molecule are either allogeneic or xenogeneic to the subject. Other pending claims are directed to compositions comprising RPE cells and cells that supply a therapeutic protein or other biologically active molecule.

For a claim to be anticipated by a reference, that reference must disclose each and every element of the claim. As the Examiner notes, Ye describes "allogeneic RPE cell transplants in the retina of rabbits" (Office Action, page 8).

Ye does not teach co-administration of RPE cells with cells that supply a therapeutic molecule, much less the co-administration of allogeneic or xenogeneic cells with RPE cells. Thus, Ye does not teach the claimed invention and, accordingly, Ye does not effectively anticipate the present invention.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §102(e)

Claims 1, 2-4, 6, 7, 9, 10, 12, 13, 16-21 and 23 were rejected under 35 U.S. C. 102(e) as allegedly being anticipated by Cherksey (U.S. Patent 5,618,531). Applicants respectfully traverse this rejection.

As described above, the present invention is directed to methods for treating a disease in a mammal by co-administering an effective amount of RPE cells to create an immunologically privileged site and an effective amount of cells to supply a therapeutic protein, or other biologically active molecule. In these methods, the co-administered cells are allogeneic or xenogeneic to the mammal. Pending claims are also directed to compositions comprising RPE cells and cells that produce a therapeutic protein, or other biologically active molecule.

Cherksey describes neural or paraneural cells, including RPE cells, attached to a matrix and administered to the brain for the treatment of Parkinson's Disease. Cherksey also describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types" (column 9, lines 3-6).

For a claim to be anticipated by a reference, that reference must disclose each and every element of the claim. Cherksey does not teach that the cells co-administered with the RPE cells (i.e., glial cells) are allogeneic or xenogeneic to the mammal to which the cells are administered nor that the RPE cells are allogeneic or xenogeneic to the co-administered cells that produce the therapeutic molecule. Thus, Cherksey does not teach the claimed invention.

Accordingly, Cherksey does not effectively anticipate the present invention.

In view of these remarks, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. §102(e).

Rejection under 35 U.S.C. §103

Claims 1-3, 14 and 15 were rejected as allegedly being unpatentable over Cherksey. Claims 1-3, 5, 7, 8 and 11 were rejected as allegedly being unpatentable over Cherksey in view of Goldstein (U.S. Patent 5,300,436). Claim 22 was rejected as allegedly being unpatentable over Cherksey in view of Selawry (1993, *Cell Transplantation* 2:123-129) and Streilein (1995, *Science* 270:1158-1159). Applicants traverse these rejections.

Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention. As discussed above, Cherksey teaches administration of matrix-attached neural and paraneural cells to the brain or spinal cord. Goldstein teaches transfecting a modified tyrosine hydroxylase gene into cells, including RPE cells, and transplantation of the genetically altered cells into the brain. Neither of these references, either alone or in combination, describes or suggests methods of treating a disease by co-administration of RPE cells and allogeneic or xenogeneic cells that supply a therapeutic protein.

As discussed above, Cherksey does not teach or suggest that cells co-administered with RPE cells are allogeneic or xenogeneic with respect to the mammal to which the cells are administered nor that the RPE cells are allogeneic or xenogeneic to the co-administered cells that produce the therapeutic molecule. Goldstein does not teach or suggest co-administration of other cells with RPE cells.

Thus, none of the references, alone or in combination, teach or suggest the claimed invention. As such, there is no motivation to combine and/or modify the cited references to arrive at the claimed invention.

Further, from the cited references, either alone or combined, one of skill in the art would have no expectation of success of the claimed invention, that is, the treatment of a disease through the co-administration of RPE cells and allogeneic or xenogeneic cells that supply a therapeutic protein.

With regard to rejection of claim 22 based on Cherksey in view of Selawry and Streilein, Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention. The cited references do not teach or suggest the claimed invention, a compartmentalized kit with RPE cells and pancreatic islet of Langerhans cells.

The teachings of Cherksey have been described above. Cherksey does not mention pancreatic islet of Langerhans cells, much less a kit with such cells and RPE cells. Selawry describes transplantation of pancreatic islet of Langerhans cells with Sertoli cells but does not mention RPE cells. Streilein describes immune-privileged sites and tissues and states that survival of testis cell grafts in nonprivileged sites "correlates with constitutive expression of FasL on Sertoli cells" (emphasis added, page 1158, column 2, first full paragraph).

Thus, none of the cited references, either alone or in combination, teach or suggest the claimed invention.

The Examiner states that "[m]otivation to combine the references is provided by Streilein by stating RPE cells and Sertoli cells can both be used to create immune privileged sites because they both secrete FasL (page 1158, column 2, first full paragraph)" (Office Action, page 11). This is not stated in Streilein. Streilein makes no statements with regard to RPE cells and FasL secretion. Streilein only refers to Sertoli cells and RPE cells together when he lists Sertoli cells and retinal pigment epithelium as examples of privileged tissues that are characterized by "intratissue structural barriers, such as extensive tight junctions among parenchymal cells" (page 1158, third column, first full paragraph).

Other than from impermissible hindsight from Applicants' specification, there is no motivation to combine and/or modify the references to arrive at the present invention of claim 22.

In sum, the Examiner has not established a *prima facie* case of obviousness.

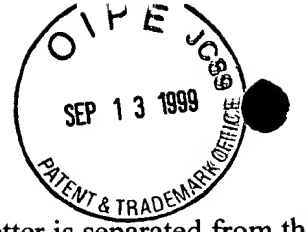
Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

References not relied upon

Enclosed with the Office Action were copies of the publications Nagineni et al. (1994) *Clin. Diagn. Lab. Immunol.* 1:569-577 and Enzmann et al. (1998) *Acta Anat. (Basel)* 162:178-183. Neither of these publications was listed in the Notice of References Cited or the Information Disclosure Statement, nor were they mentioned in the Office Action. Applicants agree that these references do not impact the patentability of the present invention. Should the Examiner request, Applicants would be willing to submit a Supplemental Information Disclosure Statement to indicate that these references have been considered.

III. CONCLUSIONS

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' attorney at the telephone number below.



In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 8, 1999

By: _____

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